Future options

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Future options: the potential role of proton irradiation

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KEYWORDS

breast cancer
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ABBREVIATIONS

ALARA = as low as reasonable achievable
LINAC = Linear accelerator
OAR = Organs at risk
Gy = Gray
IMN = internal mammary nodes
IMRT = intensity modulated radiotherapy
VMAT = volumetric-modulated arc therapy
RCTs = randomized controlled trials
RadCom = Radiotherapy Comparative
NTCP = normal tissue complication probability

ABSTRACT

Because of its physical properties, proton irradiation should be the treatment of choice for loco regional irradiation of breast cancer patients.
Conventional irradiation usually with photons has improved in the past decades reducing the dose to the organs at risk like the heart and the lungs. Still due to the properties of photons the organs at risk get unintended dose. Protons are charged particles and are able to deliver the dose to a specified depth where they stop and therefore no exit dose like in photon irradiation. This is the so-called Bragg Peak.
Although in recent years there has been a clear increase in the number of proton facilities, the availability remains scarce and the costs high. The increased availability and improvement in delivery techniques have let to more interest in the applicability for breast cancer patients. The most important challenge is how to select patients that most benefit from this new technique.
Irradiated breast cancer patients are at increased risk to develop cardiac and pulmonary toxicity and have more chance to develop secondary tumors. The advantages of dose reduction achieved by using proton irradiation or any other technique can be quantified by using data on dose effects relation for the toxicity of interest.
Patients that most benefit from proton irradiation can be selected by the model based approach (the Dutch model). This model based approach quantifies the risk reduction based on the difference in dose to the organ of interest between photon and proton irradiation.

Highlights

Dosimetric all breast cancer patients benefit from proton irradiation (As low as reasonable achievable (ALARA))
Not all breast cancer patients have clinical relevant benefit from proton irradiation
Appropriate selection criteria needs to be applied to select breast cancer patients that can benefit the most from proton irradiation

Introduction

Irradiation as part of breast cancer treatment has contributed to both improvements in local control as well as survival. Traditionally breast cancer patients have been treated with x-rays, exposing patients to the risks of dose outside of the target (the breast, chest wall and or regional nodes). Although the use of proton irradiation in cancer treatment is not new for the treatment of breast cancer there is limited data available. With the increased availability and improvements in delivery techniques there is more interest in the applicability of proton irradiation for breast cancer patients.

This article will review the potential role of proton irradiation in breast cancer patients.

Photons versus protons

Contemporary external irradiation with photons (x-rays) is delivered by a linear accelerator (LINAC). The delivered energy increases after contact with the surface (skin) reaching a maximum beneath the skin and decreasing the delivered energy the further it travels through the body. This means that photons do not stop but slow down when passing through the body. On the contrary protons do stop and have no exit dose. Protons are charged particles generated by a particle accelerator (cyclotron/cynclotron). Based on the energy, protons stop at a specific depth and deliver all their energy this is the so called Bragg peak. In order to cover a tumor adequately Bragg peaks of several energies are delivered resulting in a spread out Bragg peak. Figure 1 gives a graphic representation of the relation between relative dose deposition and distance in the body for photons and protons.

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Organs at risk (OAR)

In breast cancer irradiation the target is either the breast or chest wall with or without one or more regional lymph node regions. Given the anatomical relation of the organs at risk like lungs, heart and esophagus located dorsally to the target makes it extremely interesting to use a delivery technique without an exit dose.

The occurrence of radiation induced late effects, which can be considered as an accelerated aging process, shows no plateau phase presenting even years after treatment. The younger a patients the more years at risk for developing radiation induced side effects. The threats of long term side effects are a major burden for the cured patients.

It has been shown that at 15 years of follow-up, patients treated for left-sided breast cancers have a 1.58 times increased risk for cardiac death compared to right-sided breast cancer patients [1]. More recent data show that each Gray (Gy) increase in mean heart dose correlates with a 7.4% increase in risk of a major acute coronary event [2]. This risk is even higher in the first nine years of follow up [2,3]. In addition, on top of surgery and irradiation, an increasing number of patients are treated with cardiotoxic systemic therapies such as anthracyclines and trastuzumab. Boekel et al. have shown that irradiation to the internal mammary chain (IMN) in combination with anthracycline-based chemotherapy significantly increases the risk of cardiovascular diseases like ischemic heart disease, heart failure and valvular heart disease [4]. One of the other long term side effects of irradiation is secondary tumor induction. Compared to non-irradiated breast cancer patients, patients irradiated for breast cancer have a 1.66 times increased risk for developing lung cancer and a 2.17 increased risk of esophageal cancer [5]. Irradiation for breast cancer in women less than 40 years is associated with a 2.5 times increased risk to develop a contralateral breast cancer [6].

The risk of developing irradiation-induced side effects correlates with irradiation dose and irradiated volume, it is therefore important to attempt to reduce the irradiation dose and volume to the OAR [7].

Plan comparison

The last decade, major achievements have been made to reduce the dose to the most critical structures, including the lung, the heart and the contralateral breast. With modern radiation delivery techniques, intensity modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), tomotherapy either or not combined with breath hold techniques, it is possible to significantly reduce the dose to the most critical anatomical structures. However, despite the technological improvements, there are still a small proportion of patients that remains at a relatively high risk for developing treatment related side effects. Moreover, although with IMRT and VMAT the dose to the most critical structures can be significantly reduced, reduction of dose to a specific OAR will consequently result in spreading the dose to other parts of the body due to the physical properties of photons, resulting in an increase of the so-called integral dose, which correlates with the risk of radiation-induced secondary tumors.

Several plan comparison studies have shown that with proton irradiation the dose to heart and lung can be reduced without compromising target coverage as compared to external beam photon irradiation [8–12]. Furthermore with proton irradiation the dose to the contralateral breast is lower [8,11] than with photons which is especially relevant in the younger patients. The magnitude of the benefit of proton irradiation depends on the laterality, patients anatomy, extensiveness of the target (including loco regional node irradiation) and total prescribed dose. The superiority of proton irradiation is more pronounced in targets comprising more extensive nodal irradiation including the IMN for which with proton irradiation the volume of the heart receiving 22.5 Gy or more can be reduced by a factor 20 [12] compared to photon irradiation. In more contemporary series of photon irradiation the heart dose if treating the IMN is much lower than in older series with a median mean of around the 2.0 Gy [13] still 50% of the patients will have a mean heart dose higher than 2 Gy. Although regional node irradiation has proven to reduce breast-cancer mortality [14,15] radiation oncologists are reluctant [15] to include the IMN because of the increased heart dose and expected increased cardiac toxicity. With proton irradiation adding the IMN to the irradiation fields will only slightly increases the mean heart dose from 0.3 (+/−0.3) to 0.4 Gy (+/−0.3) [16] which is still much lower than in most photon irradiation without IMN.

Availability and cost effectiveness

Although all patient dosimetric benefit from proton irradiation most patients will have no clinical benefit. Improved treatment delivery techniques has considerable decreased the dose to the heart and lung

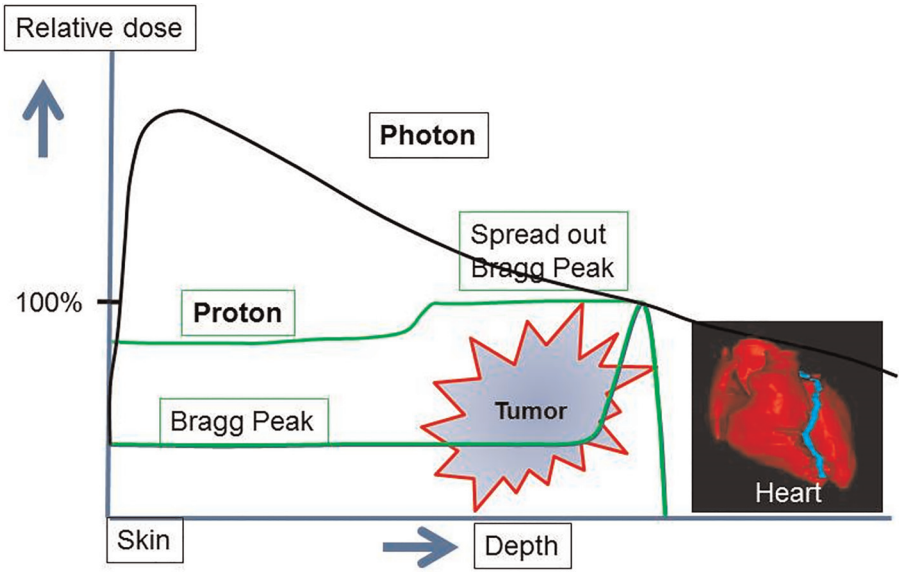

Fig. 1. Graphic representation of the relation between relative dose and distance in the body. On the Y-axis the relative dose and on the X-axis the depth into the body. In green the proton dose and in black the photon dose. The heart symbolizes an organ at risk.

[13]. A substantial part of the breast cancer patients are low risk patients and will be candidates for no irradiation or partial breast irradiation either with external beam, intraoperative irradiation or brachytherapy, which will result in lower dose compared to whole breast irradiation.

According to older estimates the cost of proton irradiation is around 1.7 to 2.4 times more than that of photon irradiation [17]. In cost-effectiveness analyses proton irradiation shows to be cost-effective in well selected breast cancer patients at increased risk for cardiovascular toxicity [18]. The costs for partial breast proton irradiation compares favorably to the costs of brachytherapy for accelerated partial breast irradiation [19].

Accessibility to proton irradiation is increasing but is still scarce. In 2015 there were worldwide 7563 photon facilities [20] compared to 48 particle therapy facilities at the end of 2014 [21]. Furthermore in 2015 only two of the 11 European centers were treating breast cancer patients [22]. By 2019 an increased number of facilities are operational of which three facilities in the Netherlands and all three are treating breast cancer patients.

Clinical data

There are no results of randomized controlled trials (RCTs) comparing proton to photon irradiation in breast cancer patients. At present there are two RCT's registered in ClinicalTrials.gov the Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial (NCT02603341) with primary endpoint reduction in major cardiovascular events and the NCT02783690 comparing two fractionation schemes in proton irradiation. Due to the lack of equipoise, based on the fact that proton irradiation results in less or no dose to the OAR as compared to photon irradiation, makes it difficult to run trials investigating the benefit of proton (dose reduction) for the reduction of treatment related toxicity.

Although scarce there is some clinical data on the use of proton irradiation for breast cancer.

In the United States National Cancer Database from 2004 to 2014 there were 871 (0.12%) patients registered as having received proton irradiation for breast cancer compared to 723,621 patients that received non proton irradiation [23]. In the proton irradiated patients 58.3% were stage 0–1 which is questionable whether these patients will benefit most from proton irradiation.

In total 12 studies [24–35] report there clinical outcomes of which three pairs of studies are (partially) based on overlapping patient populations. Table 1 summarizes all the published clinical data.

In general proton irradiation is feasible and well tolerated except twice daily accelerated partial breast for which higher rates of late skin toxicity as compared to photon irradiation.

Table 1
Study characteristics of papers published on clinical results.

First author	Publication year	Follow-up (months)	Number of patients	Treatment	Population	Fractionation	Acute toxicity	Conclusion
Luo* [24]	2019	35	42	Pr	M	45 Gy/25 fr + 5.4 Gy/3 fr	No grade 3 skin reaction.	Excellent locoregional control rates and favorable toxicity profile.
Teichman# [25]	2018	78	129 Pr = 72	Pr (APBI) versus Ph (WB)	B	P 40 Gy/10 fr Ph 50 Gy/25 fr + 10 Gy/5 fr	NR	Improved overall QoL compared to standard whole breast treatment.
Liang [26]	2018	NR	23	Pr	B + M	50 Gy/25 fr or 50.4 Gy/28 fr	43% grade 3 skin reaction.	Prognostic factors for grade 3 skin reaction.
Verma [27]	2017	15.5	91	Pr	B + M	50.4 Gy/28 fr +/– 20 Gy/5 fr	5% grade 3 skin reaction.	Acceptable toxicity in the setting of comprehensive regional nodal irradiation.
Mutter [28]	2017	NR	12	Pr	M	50 Gy/25 fr	8.3% grade 3 skin reaction.	Feasible in patients with expanders.
Bradley [29]	2016	20	18	Pr +/– combined with Ph	B + M	50.4 Gy/28 fr +/– 10–16 Gy/5–8 fr	22% grade 3 skin reaction.	Improved target coverage for the internal mammary nodes and level 2 axilla without excessive acute toxicity.
Cuaron* [30]	2015	9.3	30	Pr	B + M	45 Gy/25 fr + 5.4 Gy/3 fr	One grade 3 reconstructive complication. No grade 3 skin reaction.	Well tolerated, with acceptable rates of skin toxicity.
Galland-Girodet^ [31]	2014	84	98 *P* = 19	Pr (APBI) versus Ph (APBI)	B	32 Gy/8 fr BID	NR	Local failure rates of Ph (APBI) and Pr (APBI) similar. Pr (APBI) delivered in this study higher rates of long-term skin toxicities.
Bush# [32]	2014	60	100	Pr (APBI)	B	40 Gy/10 fr	No grade 3 skin reaction.	Excellent ipsilateral breast recurrence-free survival with minimal toxicity.
Chang [33]	2013	59	30	Pr (APBI)	B	30 Gy/6 fr	3% grade 3 skin reaction.	Excellent disease control and tolerable skin toxicity.
MacDonald [34]	2013	6	12	Pr	M	50.4 Gy/28 fr	No grade 3 skin reaction.	Postmastectomy Pr irradiation is feasible and well tolerated.
Kozak^ [35]	2006	12	20	Pr (APBI)	B	32 Gy/8 fr BID	22% grade 3 skin reaction.	Good-to-excellent cosmetic outcome. Significant acute skin toxicity.

*, #, ^overlapping treatment populations.
Abbreviations: Pr = proton, Ph = photon, NR = not reported, APBI = accelerated partial breast irradiation, Gy = Gray, M = mastectomy, B = breast conserving surgery, fr = fractions, BID = bis in die (twice daily), QOL = quality of life.

Model based approach and selection protocol in the Netherland

The model based approach (The Dutch model) [36] can be used to select patients that most benefit from proton irradiation or even for selection of patient for other innovative irradiation strategies aiming at toxicity reduction. The backbone of the model based approach is models describing the relation between dose volume parameters to an OAR at risk and the chance to develop the toxicity of interest. This is the so called normal tissue complication probability (NTCP). NTCP's are based on clinical toxicity data, preferably prospectively acquired, in relation to the dose as delivered to the patient. Changing the dose to the OAR's can result in a higher or lower NTCP value in this way the treatment plan can be optimized to make the chance of toxicity as low as possible. Based on the models one can quantify whether reducing the dose to the OAR with proton irradiation translates into an expected clinical relevant reduction in toxicity. The model-based approach has been approved by the Dutch health authorities as a valid methodology to select adult patients for proton irradiation. Prospective data registration is a prerequisite of this approval in order to validate the models in proton irradiated patients. Another condition in order to apply the model based approach is that national tumor site specific protocols with validated models must be developed. Thresholds for absolute NTCP differences for clinical relevant endpoints have been defined based on the severity of the toxicity. The higher the toxicity severity grade the lower the threshold value for selection.

In the Netherlands the model based approach has been implemented for the selection of breast cancer patient for proton irradiation. The only validated endpoint is major coronary event based on the model by Darby et al. [2]. The risk of major coronary events increases linearly with the mean dose to the heart by 7.4% per Gy [2]. The individual baseline lifetime risk is based on the national cardiac statistics and takes into account age, sex and presence or absence of a cardiac risk factor. The absolute excess risk is calculated by subtracting the individual risk, based on the mean heart dose in the photon treatment plan, from the baseline cardiovascular risk (no irradiation). If the threshold of 2% is reached the patients qualifies for a plan comparison with proton. Patients with in the plan comparison a difference in risk for major coronary event equal or larger than 2% in the advantage of the proton plan are eligible for proton irradiation treatment reimbursement. In general this will be younger patients or patients with cardiovascular risk factors in which higher dose to the heart is expected. This higher dose to the heart can be expected in left sided breast cancer patients for which loco regional irradiation including IMN is indicated and or patients with special anatomical variation like a pectus excavatum.

Conclusions

Most breast cancer patient will benefit dosimetrically from proton irradiation. Yet not all patients will have a clinical relevant advantage of proton irradiation. Because of the limited availability and higher cost it is important to select the patient that will most probably benefit from this newer dose reducing technique.

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